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PREVENTION OF SUDDEN CARDIAC DEATH BY THE ATYPICAL NEUROLEPTIC ACEPROMAZINE FOLLOWING STATUS EPILEPTICUS IN RATS

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Abstract. Normal male rats in which status epilepticus has been induced by injecting 30 mg/kg of pilocarpine after a single systemic administration of lithium (sufficient to produce blood levels of 0.2 mEq/L) invariably die within 24 hr. Real-time monitoring indicated sudden cardiac death; it was preceded by progressive intensification of arrhythmia. A single systemic injection (25 mg/kg) of the atypical phenothiazine acepromazine prevented the mortality and virtually eliminated the cardiac instability.

Key Words: acepromazine, sudden unexpected death, status epilepticus

Introduction

Between 5% and 30% of mortality within epileptic populations involve sudden unexpected death or SUD (17). SUD, unrelated to the clinical state, occurred in 6% of stroke patients admitted to an acute care unit (25). Cardiac arrhythmia is the presumed cause of death in both patient populations. At least one-quarter of patients admitted for stroke display either cardiac arrhythmias or prolongation of the QT interval (13). Cardiac arrhythmias occur in half of monitored ambulatory seizures (20) and may underlie SUD (21).

Oppenheimer et al. (21) have induced cardiac arrhythmias and sudden death in rats by making direct stimulation into the caudal insular cortices contingent upon the R component of the QRS. Cardiac instability ensued within 2 to 8 hours. This region of the insular cortices has reciprocal connections with the parabrachical nuclei and the vagal complex (nucleus of the solitary tract and the dorsal motor efferent nucleus) in the brainstem (5,15); they are the major interface of direct afferent and efferent cardiopulmonary fibers.

Status epilepticus (SE) (primary persistent but nonconclusive myoclonus), is induced within 30 minutes following a systemic 30 mg/kg injection of the muscarinic agent pilocarpine if lithium (3 mEq/kg) has been administered in a similar manner 24 hrs previously; this concentration (16) produces lithium blood levels well below (0.2 mEq/L) that suggested for maintenance of manic patients (0.8 mEq/L to 1.2 mEq/L). The SE is almost always fatal and most rats die within 24 hrs (15,27); the asymptote in the mortality curve occurs within four days (3,23,24,28).

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A single sub. cu. injection of the phenothiazine acepromazine has been shown to reduce the mortality of male rats from >95% to less than 20% if it is administered within 1 hr after the onset of SE (3,23); neither chlorpromazine nor haloperidol display any prophylactic effects (24). Acepromazine was dropped from the pharmaceutical repertoire for human practice during the 1950s because it did not produce the benefits of other phenothiazine derivatives (although it is still used in veterinarian medicine as a tranquilizer for large animals). Because the threshold for lithium/pilocarpine mediated seizures is raised by D1 dopamine receptor antagonists (2) but lowered by D2 receptor blockers, we have suspected that acepromazine is also a strong, specific D1 receptor antagonist (12). Many of the behaviors that follow acepromazine-promoted recovery from status epilepticus, especially the transient anorexia, altered palatability thresholds and incessant gnawing, are specific to D1 receptor stimulation (6,18,19); the role of possible anticholinergic effects are less likely since SE rats treated by acepromazine display mild hypothermia.

We have postulated that the SUD in rats following lithium/pilocarpine-induced SE is triggered within the strongly dopaminergic (4,8) central (Ce) amygdaloid nucleus (which is never damaged by these seizures) by the normally enhanced muscarinic effects (14) and by aberrant activity as it is gradually disinhibited from intraamygdaloid control by the insidious, cholinergic-mediated necrosis in the surrounding (primarily basolateral complex) nuclei. This activation stimulates its descending pathways to the cardiovascular centers in the brain stem (5,8,15). Our working hypothesis is that the resulting desynchrony between the inputs to the vagal complex from the insular cortices (21) and central amygdaloid nucleus would increase the risk of arrhythmia and sudden cardiac death.

Because the SUD evoked by either continuous R wave-triggered stimulation of the insular cardiac chronotropic center or the lithium/pilocarpine-induced status epilepticus requires several hours, the precipitating mechanisms must involve circumlocutious routes, progressive increase in transmitter release and cumulative stimulation of specific receptor sites (otherwise death should occur more quickly). The time course of the progressive severity of the arrhythmia is compatible with the gradual loss of inhibitory control over the central nucleus and the reduction in GABA release from striatal and nigral structures (1). However, the possibility that the acepromazine directly affects peripheral dopaminergic mechanisms in the myocardium (27) cannot be excluded.

On the basis of these previous experiments, we predicted that: (1) SUD associated with lithium/ pilocarpine-induced SE would be associated with arrhythmia and sudden cardiac cessation that is mediated through D1 receptors: (a) within the functional and structural continuum that includes the central nucleus of the amygdala, the sublenticular substantia innominata, bed nucleus of the stria terminalis, the ventromedial nucleus accumbens or its ventral striatal extensions (19) and (b) upon the presynaptic terminals of the powerful striatonigral GABA system (stimulation of the latter D1 receptor would reduce GABA release and facilitate the descending spread of paroxysmal discharges (10)) and (2) acepromazine would reduce or prevent these perturbations.

Methods

A total of 40 100- to 140-day old male Wistar rats were injected sub. cu. with 3 mEq/kg of lithium and then 4 hr or 24 hr later with 30 mg/kg of pilocarpine. About 30 min later, after the rats had displayed a brief sequence of forelimb clonus, rearing, and falling and subsequently entered SE, their ventral surfaces were shaved. They were then placed in standard plastic restraint devices. Electrodes were attached over the heart by EC2 paste and maintained by tape. Heart rate was recorded continuously during the next 24 hr by microcomputer; time "0" began the minute the acepromazine was injected (5 min after myoclonus onset). During the course of the experiment 20 rats were injected sub. cu. (neck) with 25 mg/kg of acepromazine (Atravet) while the other 20 rats were injected with saline or not injected. The mean HR for every successive 10 min block (bin time) was calculated and plotted automatically; for about half the numbers of rats from each group real time HR was collected for 10 to 15 sec on strip chart paper once every hour. Random intermittent inspection verified the mild myoclonic status (they were inhibited by the restraint); there were never any tonic-clonic convulsions. Only one rat was measured

per 24 hr period; the acepromazine and placebo treatments were randomized over the 40 days of the experiment. All rats entered their dark cycle within about 1 hr of the seizure induction.

Results

The results of the study were clear. As expected from previous observations, 90% of the rats in which SE had been induced by lithium/pilocarpine died suddenly within 24 hr. Following periods of excursions in HR, cessation of heart rate was sudden (example Figure 1A). The low HR during the last 10 min bin before the flatline is an expected artifact since the computer averaged rates every 10 min interval; consequently if the heart rate had stopped suddenly during the third min of the bin, the mean HR would be extremely low. (Occasional extreme excursions, e.g., >600 BPM, were found to be artifacts of the computer counting both P and QRS (instead of the latter only); because the purpose of the study was to determine sudden vs gradual heart failure, this integration artifact was not considered critical.) An example of the emergent arrhythmia, as measured by real time EKG, is shown in Figure 2.

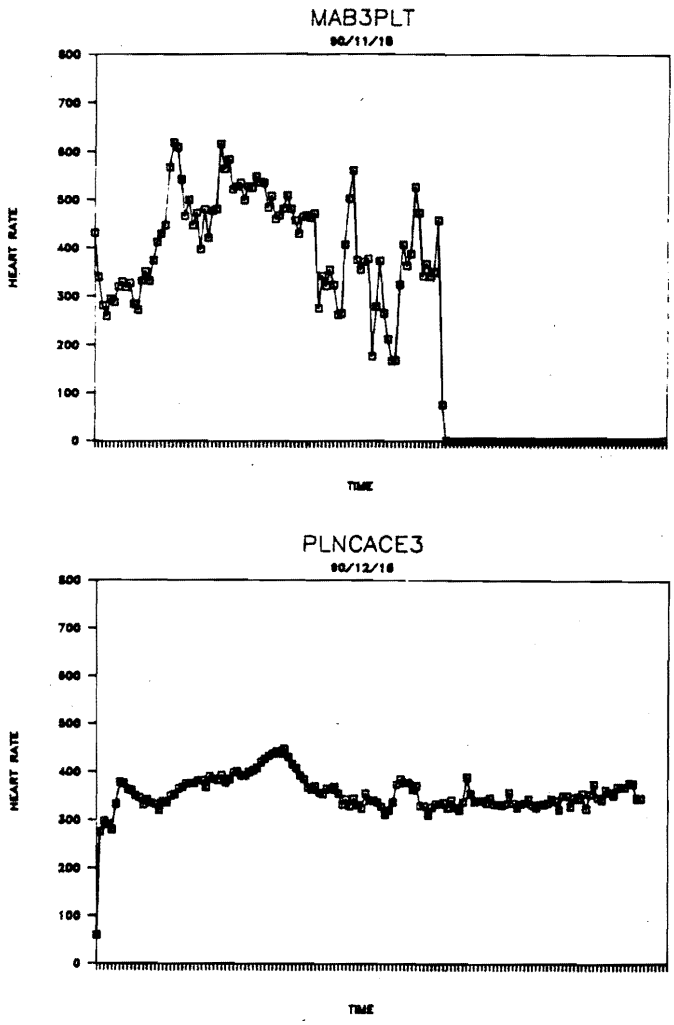

Fig. 1
Examples of mean heart rate (beats/min) over successive 10 minute blocks for rats with status epilepticus that had been induced by lithium-pilocarpine. (A): no acepromazine, (B) a single injection of acepromazine.

On the other hand, rats in which SE had been induced by the lithium/pilocarpine but was then treated with the single injection of acepromazine (25 mg/kg) showed greater cardiac stability over time; all 20 rats recovered from SE and survived (chi-squared=32.65, $p < .001$) for at least 6 days (the inflection point for cumulative mortality curves (3)). Figure 1B shows the mean HR per 10 min block of a typical rat. The average HR was within the range expected for the normally restrained rat. Note that the periods of sudden instability in HR were remarkably reduced. EKGs indicated that arrhythmia in the acepromazine treated rats was conspicuously reduced in both severity and incidence compared to non-treated animals.

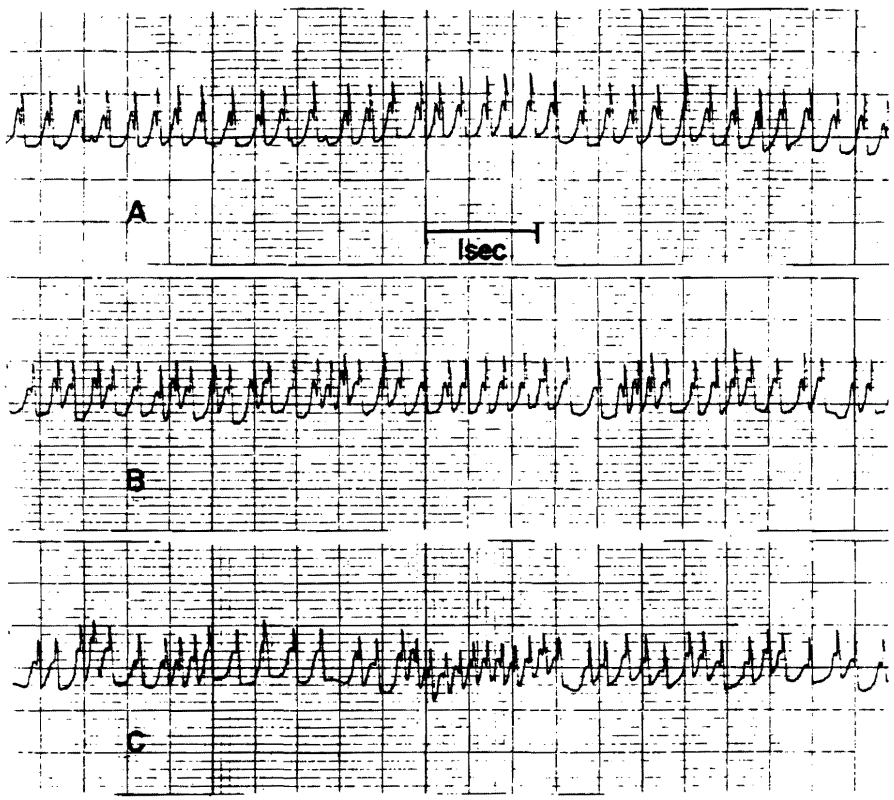

Fig. 2
Successive increase in arrythmia and tachycardia in a (sample) rat in which limbic status epilepticus had been induced by lithium-pilocarpine (no acepromazine). A): 1 hr, B) +4 hr; C) + 6 hr, after seizure induction.

Discussion

Our results support previous work that a single injection of acepromazine minimizes (23,24) the inevitable mortality that occurs following the lithium/pilocarpine-induced SE. The efficacy is optimal if the treatment is given within 1 hr after the onset of SE, although some prophylactic effect is still apparent if treatment is given within 6 hours. Death and cardiac arrhythmia are also reduced with dosages as low as 15 mg/kg of acepromazine (24). We have not yet evaluated the effects of smaller, serial dosages of this drug upon either mortality or cardiac arrythmia.

The results also indicated that acepromazine attenuates the periods of arrythmia that insidiously increase in severity and incidence after the onset of SE. The time-course and pattern of these transient cardiac aberrations are very similar (Figure 2) to those evoked by continuous (EKG) R wave-dependent triggering of electrical impulses to the insula (20,21). Although we suspect that cumulative desynchrony between the discharges from the insular and central amygdaloid regions is the likely mechanism for the SUD, we

cannot exclude the possibility that the arrythmia evoked by insular stimulation could be mediated through its direct connections with the Ce amygdaloid nucleus (7); whereas its stimulation in the normal brain produces primarily variability in heart rate and blood pressure, damage within adjacent amygdaloid nuclei, induced by a partial complex seizure history (23,24), could encourage the escalation of paroxysmal discharges through this pathway. It may be relevant that the first two layers of the caudal insular cortex receive a dense supply of dopaminergic fibers from the ventral tegmentum (9).

In partial complex epileptic patients, who are most prone to SE (11,17), diffuse drop out occurs within the amygdaloid region of more than 25% of the patients. Against this necrosis, there is a preferential survival of amygdaloid (and hippocampal) neurons whose firing patterns are synchronous with the cardiac cycle (11). Occasional supranormal recruitment of these neurons could promote indigenous burst firing and propagation to the central amygdaloid nucleus and/or insula. Such mutual interaction is more likely in the human brain considering the reciprocal amygdaloinsular connections (7,22). A variety of triggers, from amygdaloid burst-firing associated with transient, mild hypoxia to vasospasm within any of the several branches of the middle cerebral artery that overlay the insula, could develop.

Reduction in central dopamine binding to Dl receptors is one likely mechanism by which this form of cardiac arrythmia and sudden death could be blocked. The effect may be due to the specific blockade of telencephalic cardiovascular pathways or by the reversal of electrocortical suppression; Dl but not D2 receptor antagonists are known to partially reverse barbiturate anaesthesia. It is associated with a significant increase in the power frequency of the EEG spectrum (26). If our results are generalizable to human beings, then treatment within the first 1-2 hours of limbic status epilepticus with a Dl receptor blocker could attenuate the gradual escalation of arrhythmia that leads to SUD.

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